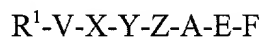


IT IS CLAIMED:

1. A crystalline protein composition containing a  $\beta$ -secretase inhibitor molecule wherein the inhibitor is a compound of formula I:



5

(I)

wherein V, A, E and F are valine, alanine, glutamine and phenylalanine respectively including conservative substitutions thereof;

$R^1$  is chosen from hydrogen, acetyl, *t*-butoxycarbonyl and carbobenzoyl;

10

X is chosen from methionine, phenylglycine, n-leucine (n-Leu), asparagine, phenylalanine, glycine and valine;

Z is chosen from valine,  $\alpha$ -aminobutyric acid (Abu), phenylglycine (Phg) and alanine; and

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Y is statine, acha (cyclohexylmethylstatine) or phenylstatine (Phe-sta) wherein the phenyl group may optionally have mono or di-substitution chosen from the group consisting of Cl, F, Br, methyl and methoxy.

20

2. The crystalline protein composition of claim 1, wherein said  $\beta$ -secretase inhibitor is chosen from the group consisting of  $R^1$ -VMStaVAEF; Ac-VPhgStaVAEF;  $R^1$ -Vn-Leu-Sta-VAEF;  $R^1$ -VNStaVAEF;  $R^1$ -VFStaVAEF;  $R^1$ -V MPhe-staVAEF.

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3. The crystalline protein composition of claim 2, wherein in said  $\beta$ -secretase inhibitor  $R^1$  is H or acetyl.

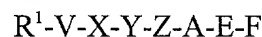
30

4. The crystalline protein composition of claim 3, wherein in said  $\beta$ -secretase inhibitor  $R^1$  is acetyl.

5. The crystalline protein composition of claim 3, wherein said  $\beta$ -secretase inhibitor is Ac-VMStaVAEF.

35

6. A compound capable of inhibiting  $\beta$ -secretase wherein the compound is of formula I:



## (I)

wherein V, A, E and F are valine, alanine, glutamine and phenylalanine respectively including conservative substitutions thereof;

R<sup>1</sup> is chosen from hydrogen, acetyl, t-butoxycarbonyl and carbobenzoyl;

5 X is chosen from methionine, phenylglycine, n-leucine (n-Leu), asparagine, phenylalanine, glycine and valine;

Z is chosen from valine, α-aminobutyric acid (Abu), phenylglycine (Phg) and alanine;

and

10 Y is statine, acha (cyclohexylmethylstatine) or phenylstatine (Phe-sta) wherein the phenyl group may optionally have mono or di-substitution chosen from the group consisting of Cl, F, Br, methyl and methoxy.

7. The compound of claim 6, wherein said β-secretase inhibitor is chosen from the group consisting of R<sup>1</sup>-VMStaVAEF; Ac-VPhgStaVAEF; R<sup>1</sup>-V n-Leu-Sta-VAEF; R<sup>1</sup>-  
15 VNStaVAEF; R<sup>1</sup>-VFStaVAEF; R<sup>1</sup>-V MPhe-staVAEF.

8. The compound of claim 7, wherein in said β-secretase inhibitor R<sup>1</sup> is H or acetyl.

9. The compound of claim 8, wherein in said β-secretase inhibitor R<sup>1</sup> is acetyl.

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10. The compound of claim 9, wherein said β-secretase inhibitor is Ac-VMStaVAEF.

11. A crystalline protein composition containing a β-secretase inhibitor molecule wherein the inhibitor is a compound of formula II:

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## (II)

wherein V, A, E and F are valine, alanine, glutamine and phenylalanine respectively including conservative substitutions thereof;

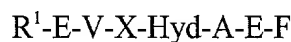
R<sup>1</sup> is chosen from hydrogen, acetyl, t-butoxycarbonyl and carbobenzoyl;

30 X is chosen from methionine, phenylglycine, n-leucine (n-Leu), asparagine, phenylalanine, glycine and valine;

and Hyd is hydroxyethylene.

12. The crystalline protein composition of claim 11 wherein said  $\beta$ -secretase inhibitor is R<sup>1</sup>-EVMHydAEF.

5 13. A compound capable of inhibiting  $\beta$ -secretase wherein the compound is of formula II:



(II)

wherein V, A, E and F are valine, alanine, glutamine and phenylalanine respectively

10 including conservative substitutions thereof;

R<sup>1</sup> is chosen from hydrogen, acetyl, *t*-butoxycarbonyl and carbobenzoyl;

X is chosen from methionine, phenylglycine, n-leucine (n-Leu), asparagine,

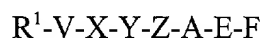
phenylalanine, glycine and valine;

and Hyd is hydroxyethylene.

15

14. The compound of claim 13 wherein said  $\beta$ -secretase inhibitor is R<sup>1</sup>-EVMHydAEF.

15. A method of screening for compounds that inhibit A $\beta$  production, comprising measuring the binding of a purified  $\beta$ -secretase polypeptide with a  $\beta$ -secretase inhibitor  
20 compound of formula I



(I)

wherein V, A, E and F are valine, alanine, glutamine and phenylalanine

respectively including conservative substitutions thereof;

25

R<sup>1</sup> is hydrogen, acetyl, *t*-butoxycarbonyl or carbobenzoyl;

X is methionine, phenylglycine, n-leucine (n-Leu), asparagine, phenylalanine, glycine or valine;

Z is valine,  $\alpha$ -aminobutyric acid (Abu), phenylglycine (Phg) and alanine;

and

Y is statine, acha (cyclohexylmethylstatine) or phenylstatine (Phe-sta) wherein the phenyl group may optionally have mono or di-substitution chosen from the group consisting of Cl, F, Br, methyl and methoxy,

in the presence of a test compound, and selecting the test compound as a  $\beta$ -secretase active-site binding compound, if binding of the inhibitor in the presence of said test compound is less than binding of the inhibitor in the absence of said test compound.

16. The method of claim 15, wherein said  $\beta$ -secretase inhibitor is chosen from the group consisting of  $R^1$ -VMStaVAEF; Ac-VPhgStaVAEF;  $R^1$ -Vn-Leu-Sta-VAEF;  $R^1$ -VNStaVAEF;  $R^1$ -VFStaVAEF;  $R^1$ -V MPhe-staVAEF.

17. The method of claim 16, wherein in said  $\beta$ -secretase inhibitor  $R^1$  is H or acetyl.

18. The method of claim 17, wherein in said  $\beta$ -secretase inhibitor  $R^1$  is acetyl.

19. The method of claim 18, wherein said  $\beta$ -secretase inhibitor is Ac-VMStaVAEF.

20. A method of screening for compounds that inhibit  $A\beta$  production, comprising measuring the binding of a purified  $\beta$ -secretase polypeptide with a  $\beta$ -secretase inhibitor compound of formula II



(II)

wherein V, A, E and F are valine, alanine, glutamine and phenylalanine respectively including conservative substitutions thereof;

$R^1$  is chosen from hydrogen, acetyl, *t*-butoxycarbonyl and carbobenzoyl;

X is chosen from methionine, phenylglycine, n-leucine (n-Leu), asparagine, phenylalanine, glycine and valine;

and Hyd is hydroxyethylene

in the presence of a test compound, and selecting the test compound as a  $\beta$ -secretase active-site binding compound, if binding of the inhibitor in the presence of said test compound is less than binding of the inhibitor in the absence of said test compound.

21. The method of claim 20 wherein said  $\beta$ -secretase inhibitor is R<sup>1</sup>-EVMHydAEF.

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